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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/773,761	02/06/2004	Mark G. Erlander	022041-001420US	5596

70680 7590 05/28/2009

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EXAMINER
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ART UNIT	PAPER NUMBER
1637	

MAIL DATE	DELIVERY MODE
05/28/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/773,761	ERLANDER ET AL.	
	Examiner	Art Unit	
	ANGELA BERTAGNA	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 May 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-38,42,49,50,52-63 and 67-70* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-38,42,49,50,52-63 and 67-70* is/are rejected.

7)☒ Claim(s) *6,7,9,14,15,17,23,24,26,32,38 and 61-63* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. Applicant's response filed on September 20, 2007 in response to the non-final rejection mailed on June 20, 2007 is acknowledged. Applicant's responses filed on June 17, 2008 and December 20, 2008 in response to the restriction requirement mailed on December 17, 2007 are acknowledged. Applicant's submission of a Supplemental Reply on May 18, 2009 is also acknowledged. This application has been re-assigned to Angela Bertagna in Art Unit 1637. The Examiner's correspondence information appears at the conclusion of this Office Action.

Claims 6-38, 42, 49, 50, 52-63, and 67-70 are currently pending. In the response, claims 6, 7, 9, 11-15, 17-21, 23, 24, 26-30, 32, 35-38, 42, 49, 50, 52-57, and 60 were amended, and claims 64-66 were canceled. Claims 67-70 are new.

The following include new grounds of rejection. Any previously made rejections or objections not reiterated below have been withdrawn. Applicant's arguments that remain pertinent to the new grounds of rejection have been fully considered, but they were not persuasive for the reasons set forth in the "Response to Arguments" section. Since not all of the new grounds of rejection presented in below were necessitated by Applicant's amendment, this Office Action is made **NON-FINAL**.

Election/Restrictions

2. Applicant's election with traverse of Group I, claims 6-31, 52-55, 58, and 61-66 in the response filed on June 17, 2008 is acknowledged. Upon further consideration, it has been determined that all of the currently pending claims can be examined without imposing an undue

burden to the Examiner. Accordingly, the restriction requirement set forth on December 17, 2007 has been **WITHDRAWN**. All of the pending claims will be examined on the merits. Since the restriction requirement has been withdrawn, Applicant's arguments filed on June 17, 2008 concerning the propriety of said requirement are moot.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Priority

3. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original non-provisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See Transco Products, Inc. v. Performance Contracting, Inc., 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

In this case, the disclosure of the prior-filed application, Provisional Application No. 60/504,087, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for all of the pending claims in the instant application. The '087 application does not provide adequate support for the requirement in all of the instant claims to determine the ratio of HoxB13 and IL17BR RNA expression levels. Accordingly, benefit of the prior-filed '087 application has not been granted, and the filing date of the parent application, 10/727,100 (**December 2, 2003**) has been used for prior art purposes.

Claim Objections

4. Claim 7 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 7 is drawn to the method of claim 6, wherein the measured RNA expression levels are indicative of the probability of cancer recurrence via metastasis or of survival outcome. The phrase "or survival outcome" broadens the scope of the claim beyond that of claim 6, which is directed to assessing the risk of cancer recurrence. Accordingly, claim 7 fails to further limit the method of claim 6.

Claims 9, 17, and 26 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 9, 17, and 26 are drawn to the methods of claims 6, 14, and 23, respectively, wherein the assaying step comprises determining

the mRNA expression levels of HoxB13 and IL17BR. Since the RNA expression levels of these genes are measured in the method of claims 6, 14, and 23, the methods of claims 9, 17, and 26 fail to further limit the methods of claims 6, 14, and 23.

Claim 6 is objected to because of the following informalities: This claim contains minor grammatical and typographical errors. The following changes are suggested.

(i) This claim appears to be missing the word "the" after the word "determine" in line 1.

(ii) Replacing the term "said subject" appearing in lines 4, 5, 8, and 9 with "said human subject" is suggested to improve consistency within the claim.

(iii) Inserting the word "RNA" in line 6 before the word "expression" is suggested to improve consistency within the claim.

(iv) Deleting the comma after the word "levels" in lines 13 and 14.

Claim 7 is objected to because of the following informalities: Replacing the term "expression level(s)" in line 1 with "RNA expression levels" is suggested to improve consistency with claim 6.

Claim 14 is objected to because of the following informalities: This claim contains minor grammatical and typographical errors. The following changes are suggested.

(i) This claim appears to be missing the word "an" or "the" after the word "determine" in line 1.

(ii) Replacing the term "said subject" appearing in line 5 with "said human subject" is suggested to improve consistency within the claim.

(iii) Deleting the comma after the word "breast cancer" in line 3 is suggested.

(iv) Inserting the word "RNA" in line 7 before the word "expression" is suggested to improve consistency within the claim.

Claim 15 is objected to because of the following informalities: Replacing the term "expression level(s)" with "RNA expression levels" is suggested to improve consistency with claim 14.

Claim 23 is objected to because of the following informalities: This claim contains minor grammatical and typographical errors. The following changes are suggested.

(i) Deleting the word "to" in line 1 is suggested to correct a typographical error.

(ii) Inserting the word "RNA" in lines 8 and 12 before the word "expression" is suggested to improve consistency within the claim.

(iii) Deleting the comma after the word "levels" in lines 12 and 13 is suggested.

Claim 24 is objected to because of the following informalities: Replacing the term "expression level(s)" with "RNA expression levels" is suggested to improve consistency with claim 14.

Claim 32 is objected to because of the following informalities: This claim contains minor grammatical and typographical errors. The following changes are suggested.

(i) The word “the” appears to be missing after the word “determine” in line 1.

(ii) Replacing “said subject” in line 4 and “said agent” in lines 9 and 14 with “said human subject” and “said antiestrogen agent” is suggested to improve consistency within the claim.

(iii) Deleting the comma after the word “sequences” in lines 5 and 10.

Claims 38 and 61-63 are objected to because of the following informalities: These claims contain minor grammatical and typographical errors. Deleting the comma after the phrase "5' untranslated region" in line 3 is suggested.

Appropriate correction is required.

Claim Rejections - 35 USC § 112, 2nd paragraph

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 32-38, 42, 56, 57, 59, 60, and 70 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 32-38, 42, 56, 57, 59, 60, and 70 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The preamble of independent claim 32 states that the method is drawn to determining the risk of cancer recurrence, but the body of the claim only recites limitations directed to assessing responsiveness to an antiestrogen agent. The claim does not relate responsiveness to the antiestrogen agent with cancer recurrence, and accordingly, the claims appear to be missing essential method steps.

Claim 42 is further indefinite, because it recites the limitation "said ratio of HoxB13 and IL17BR RNA expression levels" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 112, 1st paragraph (New Matter)

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23-31, 54, 55, 63, and 69 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Section 2163.03 of the MPEP states, "An amendment to the claims or the addition of a new claim must be supported by the description of the invention in the application as filed. *In re Wright*, 866 F.2d 422, 9 USPQ2d 1649 (Fed. Cir. 1989)."

Section 2163.05 of the MPEP states, "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)."

Claims 23-31, 54, 55, 63, and 69 contain new matter, because the original disclosure does not provide support for the amendment to independent claim 23 requiring a determination of a positive response to treatment with an antiestrogen if the ratio of HoxB13 and IL17BR RNA expression levels is higher than the average ratio of HoxB13 and IL17BR RNA expression levels in ER(+) breast cancer cells and a negative response to treatment with an antiestrogen if the ratio of HoxB13 and IL17BR RNA expression levels is lower than the average ratio of HoxB13 and IL17BR RNA expression levels in ER(+) breast cancer cells. The original disclosure only

provides support for the opposite situation (*i.e.* a positive response to treatment with an antiestrogen if the ratio of HoxB13 and IL17BR RNA expression levels is lower than the average ratio of HoxB13 and IL17BR RNA expression levels in ER(+) breast cancer cells and a negative response to treatment with an antiestrogen if the ratio of HoxB13 and IL17BR RNA expression levels is higher than the average ratio of HoxB13 and IL17BR RNA expression levels in ER(+) breast cancer cells). Accordingly, claims 23-31, 54, 55, 63, and 69 have been rejected under 35 U.S.C. 112, first paragraph for incorporating new matter.

Claim Rejections - 35 USC § 112, 1st paragraph (Enablement)

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6-38, 42, 49, 50, 52-63, and 67-70 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: (1) the nature of the invention, (2) the breadth of the claims, (3) guidance of the specification, (4) the existence of working examples, (5) state of the art, (6) predictability in the art, and (7) the amount of experimentation necessary and the relative skill levels of those in the art.

Nature of the Invention:

Claims 6-13, 49, 50, 58, 61, and 67 are drawn to a method of determining the risk of cancer recurrence in a human subject afflicted with ER(+) breast cancer based on the observed ratio of HoxB13 and IL17BR RNA expression levels.

Claims 14-22, 52, 53, 62, and 68 are drawn to a method of determining the clinical outcome of a human subject afflicted with ER(+) breast cancer an treated with an antiestrogen agent based on the observed ratio of HoxB13 and IL17BR RNA expression levels.

Claims 23-31, 54, 55, 63, and 69 are drawn to a method of predicting the response of a human subject afflicted with ER(+) breast cancer to an antiestrogen agent based on the observed ratio of HoxB13 and IL17BR RNA expression levels.

Claims 32-38, 42, 56, 57, 59, 60, and 70 are drawn to a method of determining the risk of cancer recurrence in a human subject afflicted with ER(+) breast cancer if treated with an antiestrogen agent based on the observed ratio of HoxB13 and IL17BR expression levels.

The invention is classified in the unpredictable arts of chemistry and biology.

Breadth of the claims:

The claims are extremely broad in scope. The methods of claims 6-13, 58, and 61 encompass determining the risk of cancer recurrence or clinical outcome in ER(+) breast cancer human subjects of any age, ethnic population, and gender based solely on the observed ratio of the mRNA expression levels any HoxB13 sequence and any IL17BR sequence, where any expression level ratio higher than the average ratio of HoxB13 and IL17BR RNA expression levels in ER(+) breast cancer cells is indicative of cancer recurrence. Claims 49 and 50 further

limit the HoxB13 and IL17BR sequences to SEQ ID NO: 6 and SEQ ID NO: 1, respectively. Claim 67 further limits the antiestrogen agent to tamoxifen.

Claims 14-22 and 62 encompass determining clinical outcome in human subjects of any age, ethnic population, and gender based solely on the observed ratio of the mRNA expression levels any HoxB13 sequence and any IL17BR sequence, where any expression level ratio higher than the average ratio of HoxB13 and IL17BR RNA expression levels in ER(+) breast cancer cells is indicative of cancer recurrence. The methods of claims 14-22 are also not limited to patients having ER(+) breast cancer and comprise treatment of the subjects with any antiestrogen agent. Claims 52 and 53 further limit the HoxB13 and IL17BR sequences to SEQ ID NO: 6 and SEQ ID NO: 1, respectively. Claim 68 further limits the antiestrogen agent to tamoxifen.

The methods of claims 23-31 and 63 encompass predicting the response of ER(+) breast cancer human subjects of any age, ethnic population, and gender to treatment with any antiestrogen agent based solely on the observed ratio of the mRNA expression levels any HoxB13 sequence and any IL17BR sequence, where any expression level ratio higher than the average ratio is indicative of a positive response to treatment. Claims 54 and 55 further limit the HoxB13 and IL17BR sequences to SEQ ID NO: 6 and SEQ ID NO: 1, respectively. Claim 69 further limits the antiestrogen agent to tamoxifen.

The methods of claims 32-34, 37, and 59 encompass determining the risk of cancer recurrence in human ER(+) breast cancer subjects of any age, ethnic population, and gender if treated with any antiestrogen agent based solely on any observed increase in the RNA or protein expression levels of any HoxB13 sequences (i.e. wild-type or mutant) or any observed decrease in the RNA or protein expression levels of any IL17BR sequences (i.e. wild-type or mutant).

Claims 35, 36, 38, 42, and 60 further limit the method to mRNA expression levels, and claims 56 and 57 further limit the HoxB13 and IL17BR sequences to SEQ ID NO: 6 and SEQ ID NO: 1, respectively. Claim 70 further limits the antiestrogen agent to tamoxifen.

Guidance of the specification and Working Examples:

The specification teaches that the ratio of HoxB13 and IL17BR RNA expression can be used to determine a risk of cancer recurrence, predict clinical outcome, and predict the responsiveness of any human subject to treatment with an antiestrogen agent (see pages 9-12 and 55, for example). The specification also teaches that any change in the ratio compared to the average ratio is sufficient for prediction and risk assessment (pages 17-18, for example). The specification further teaches that the methods can be used to predict the responsiveness of a subject to any antiestrogen agent (pages 15-16, for example). Finally, the specification provides a number of HOXBI3 and ILITBR sequences and teaches that "any sequence, or unique portion thereof, of the following ILI7BR sequence, identified by AF208111 or AF208111.1, may be used in the practice of the invention" and goes on to disclose the ILI7BR sequence of SEQ ID NO: 3 (see pages 34, lines 2-4 and SEQ ID NO:3 on page 34-35). Similarly, the specification teaches that "any sequence encoding all or part of the protein encoded by any ILI7BR sequence disclosed herein may be used (page 29, lines 4-10)."

In Example 1, the specification teaches that a 22,000-gene high-density oligonucleotide microarray was used to determine gene expression patterns from 60 ER+ breast cancer patients who were uniformly treated with tamoxifen (see page 60, line 20 - page 61, line 14). The ILI7BR and HOXB13 oligonucleotide sequences used in the microarray are undisclosed. In Example 2,

the specification teaches that from the resulting data set, 5,475 genes were selected for further analysis and that using this reduced dataset, a t-test was performed on each gene comparing "the tamoxifen responders and non-responders, leading to identification of 19 differentially expressed genes at the P value cutoff of 0.001 (Table 2)", including HOXBI3 and ILI7RB (see page 65, lines 5-15). Then, to further refine the analysis, the specification teaches that the same cohort was reanalyzed following laser-capture microdissection of tumor cells within each tissue section and 9 differentially expressed gene sequences were identified with P0.001, again including HOXBI3 and ILI7BR (see page 66, lines 2-6 and Table 3). The specification teaches that HOXBI3, ILI7BR, and CACNAID expression levels were found to be significantly correlative in both the LCM and whole tissue section samples (see, *e.g.*, page 67, lines 3-10). The specification further states that "...these three genes have potential utility for predicting clinical outcome of adjuvant tamoxifen therapy (page 68, lines 6-7)." Finally, the specification discloses that the HOXBI3 and ILI7BR expression ratio is a "strong independent predictor of treatment outcome in the setting of adjuvant tamoxifen therapy (see, *e.g.*, page 70, lines 5-7)."

However, the working examples do not teach the use of the HOXBI3 and ILI7BR expression ratio outside the setting of adjuvant tamoxifen therapy (*e.g.* to predict a risk of cancer recurrence or the responsiveness of a subject to any other antiestrogen agent). The specification also does not teach what levels of mRNA expression of HOXB13 and IL17BR sequences are required such that the ratio is indicative of responsiveness to a particular treatment, clinical outcome, or the risk of cancer recurrence. The working examples also do not analyze protein expression ratios of HoxB13 and IL17BR. The working examples also do not address the ability of the expression ratio to be used in different human populations (*e.g.* different ethnic

populations, age groups, or male and female breast cancer patients) or whether the ratios of any different HoxB13 and IL17BR sequences can be used to predict the risk of cancer recurrence, clinical outcome, or responsiveness to antiestrogen treatment. Finally, the working examples do not describe correlating a lower than average HoxB13/IL17BR ratio with a lack of response to antiestrogen treatment as required by claim 23.

State of the Art and Unpredictability in the Art

In general, the art is underdeveloped with respect to the use of a gene expression profiles generally (much less the use of only ILI7BR and HOXBI3 sequences) to predict breast cancer outcome.

The unpredictability of correlating gene expression level to any phenotypic quality is taught in the prior art by Wu (J. Pathol. 195(1):53-65, 2001; cited previously). Wu teaches that gene expression data must be interpreted in the context of other biological knowledge, involving various types of "post genomics" informatics, including gene networks, gene pathways, and gene ontologies (page 53, left column). The reference indicates that many factors may be influential to the outcome of data analysis, and teaches that expression data can be interpreted in many ways. The conclusions that can be drawn from a given set of data depend heavily on the particular choice of data analysis. Much of the data analysis depends on such low-level considerations as normalization and such basic assumptions as normality (page 63 - Discussion). Additionally, the post-filing art reveals that most gene association studies are typically wrong. Lucentini (The Scientist, page 20, Dec. 20, 2004; cited previously) teaches that it is strikingly common for follow-up studies to find gene-disease associations wrong (left column, 3rd paragraph).

Lucentini teaches that two recent studies found that typically when a finding is first published linking a given gene to a disease there is only roughly a one-third chance that the study will reliably confirm the finding (left column, 3rd paragraph). Lucentini teaches that bigger sample sizes and more family-based studies, along with revised statistical methods should be included in the gene association studies (middle column, 1st full paragraph).

The lack of predictive success of gene expression studies may, in part, be due to the fact that increased mRNA is not always indicative of protein expression levels. Chen et al. (Molecular and Cellular Proteomics 1:304-313, 2002; cited previously) compared mRNA and protein expression for a cohort of genes in the same lung adenocarcinomas. Only 17% of 165 protein spots or 21% of the genes had a significant correlation between protein and mRNA expression levels. Chen states that "the use of mRNA expression patterns by themselves, however, is insufficient for understanding the expression of protein products" (page 304) and "it is not possible to predict overall protein expression levels based on average mRNA abundance in lung cancer samples" (pages 311-312). Similarly, since it is well established in the art that single nucleotide substitutions can result radical alterations of gene expression, the ability of each of the different HoxB13 and IL17BR mRNA and protein sequences encompassed by the claims to function in the claimed methods is highly unpredictable.

Most significantly, the post-filing art of Ma et al. (Cancer Cell 5:607-616, 2004; cited previously) does report the use of HOXBI3 and ILI7BR to attempt to predict clinical outcome in breast cancer patients treated with tamoxifen. This study also discloses a study in which gene expression profiles of ER+ primary breast cancers treated with adjuvant tamoxifen therapy were generated (see entire document, especially the Abstract). However, Ma concluded that "[t]he

observation that a simple expression ratio of two genes, HOXBI3:ILI7BR, accurately predicts tumor recurrence in adjuvant tamoxifen-treated patient with early-stage ER-positive breast cancer is limited by the size of patient cohorts" and that it "will require confirmation in a large population-based cohort" (paragraph bridging pages 612-613). Moreover, Ma states that "it remains to be determined whether this two-gene ratio predicts a tumor's response to tamoxifen or its intrinsic aggressiveness, or both" and that a "similarly case-matched cohort of untreated patients will be required to address this issue" (ibid). This level of unpredictability is exacerbated by the fact that "little is known about the relevance of HOXBI3 in breast cancer biology", and further that "[l]ittle information exists in the literature linking ILI7BR to breast cancer" as further taught by Ma (page 611, 2nd column, first full paragraph and page 613, 1st column, 1st full paragraph).

Based on these teachings in the cited references, it must be concluded that extension of the data presented in the working examples to cover the full scope of the claim (*i.e.* analysis of other antiestrogen agents, the use of protein-based expression ratios rather than mRNA-based expression ratios, assessment of cancer risk, clinical outcome, or antiestrogen responsiveness in any human subject population, *etc*) would be a highly unpredictable undertaking.

Quantity of Experimentation

The quantity of experimentation required in this case is immense, because it would require significant study and experimentation including trials with hundreds of patients to determine that the claimed HoxB13/IL17BR RNA expression ratio is capable of reliably functioning to determine the risk of cancer recurrence, assess clinical outcome, or predict the

response of a particular human subject population to treatment with a single antiestrogen agent. The quantity of experimentation required to conduct the claimed methods would constitute an inventive, unpredictable, and difficult undertaking in itself, requiring years of inventive effort, with no guarantee of success at the conclusion. Furthermore, each of the different HoxB13 mRNA and protein sequences, IL17BR mRNA and protein sequences, antiestrogen agents, and subject populations encompassed by the claimed methods would require the same extensive trial-and-error type experimentation in order to determine its ability to be used to practice the claimed methods, since the results obtained for embodiment would not necessarily extend to any of the other embodiments encompassed by the claims.

The teachings in the prior art and the post-filing art support this conclusion regarding the quantity of experimentation required to practice the claimed methods. For example, Feng et al. (Critical Reviews in Clinical Laboratory Sciences (2006) 43(5-6): 497-560; newly cited) teaches that although discovery of promising biomarkers occurs with much less experimental effort than previously, validation of clinical utility remains slow and difficult (page 537, last paragraph). Feng stated, "Biomarker discovery may require only a few weeks and a small number of patient samples, whereas its validation may require thousands of samples from multi-center trials (page 537, last paragraph)." Srinivas et al. (The Lancet (2001) 2: 698-704; newly cited)summarizes the extensive effort required to establish the diagnostic value of even a single biomarker in a single cancer in human subject, stating at pages 702-703:

> The sensitivity, specificity, and predictive value of biomarkers have to be determined through use of body fluids, paired tumours, and surrounding tissue from a wide variety of cancers before they can be used in populations. Many samples from individuals with known characteristics should be processed, to minimize the problems of confounding and to avoid spurious associations. Before field-testing, it should be established that the biomarker is truly in the path of pathogenesis and not merely the result of an adaptive response. Case-control studies on stored samples should be used to test the efficiency of the biomarkers. Although the emerging technologies show great promise, care must be taken to

> define and establish references or baseline profiles from normal tissue, cells, or body fluids. Extensive animal studies may help refine human testing before screening. The biomarker assay should be reproducible to avoid false-positive and false-negative results and also to provide a substantial lead-time before clinical diagnosis.

Thus, the teachings in the art of Feng and Srinivas in combination with the teachings of Ma cited above support the conclusion that a large quantity of experimentation, with the use of many hundreds, perhaps even thousands, of subject samples would be necessary to practice the full scope of the claimed methods. These large sample sizes would be required for each different embodiment of the claimed methods (*i.e.* different HoxB13 sequences, different IL17BR sequences, different human populations, different antiestrogen agents, *etc*). Each set of experiments would be essentially independent from the others, and success in one set of experiments would not necessarily be predictive of success in another set of experiments. Furthermore, each set of experiments would be conducted with no guarantee of success.

The Level of skill in the art

The level of skill in the art is deemed to be high.

Conclusion

Given the complex nature of invention and the underdeveloped state of the art at the time of filing, there would be a large and prohibitive amount of experimentation required to make and use the claimed invention.

Claim Rejections - 35 USC § 112, 1st paragraph (Written Description)

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6-38, 42, 49, 50, 52-63, and 67-70 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The central inquiry when considering written description is whether an ordinary artisan would reasonably conclude that Applicant was in possession of the claimed invention at the time of filing (see MPEP 2163 and *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1566-67, 43 USPQ2d 1398, 1404-05 (Fed. Cir. 1997); *Hyatt v. Boone*, 146 F.3d 1348, 1354, 47 USPQ2d 1128, 1132 (Fed. Cir. 1998)).

According to Revision I of the Written Description Training Materials (posted 4/11/08 at http://www.uspto.gov/web/menu/written/pdf), the following factors should be considered, when evaluating a claim for compliance with the written description requirement: (a) actual reduction to practice, (b) disclosure of drawings or structural chemical formulas (c) sufficient relevant identifying characteristics (d) method of making the claimed invention, (e) level of skill and knowledge in the art, and (f) predictability in the art (see page 1 of the Training Materials).

The instant claims 6-13, 49, 50, 58, 61, and 67 are drawn to a method of determining the risk of cancer recurrence in a human subject afflicted with ER(+) breast cancer based on the

observed ratio of HoxB13 and IL17BR RNA expression levels. Claims 14-22, 52, 53, 62, and 68 are drawn to a method of determining the clinical outcome of a human subject afflicted with ER(+) breast cancer an treated with an antiestrogen agent based on the observed ratio of HoxB13 and IL17BR RNA expression levels. Claims 23-31, 54, 55, 63, and 69 are drawn to a method of predicting the response of a human subject afflicted with ER(+) breast cancer to an antiestrogen agent based on the observed ratio of HoxB13 and IL17BR RNA expression levels. Claims 32-38, 42, 56, 57, 59, 60, and 70 are drawn to a method of determining the risk of cancer recurrence in a human subject afflicted with ER(+) breast cancer if treated with an antiestrogen agent based on the observed ratio of HoxB13 and IL17BR expression levels.

The claims are extremely broad in scope. The methods of claims 6-13, 58, and 61 encompass determining the risk of cancer recurrence or clinical outcome in ER(+) breast cancer human subjects of any age, ethnic population, and gender based solely on the observed ratio of the mRNA expression levels any HoxB13 sequence and any IL17BR sequence, where any expression level ratio higher than the average ratio of HoxB13 and IL17BR RNA expression levels in ER(+) breast cancer cells is indicative of cancer recurrence. Claims 49 and 50 further limit the HoxB13 and IL17BR sequences to SEQ ID NO: 6 and SEQ ID NO: 1, respectively. Claim 67 further limits the antiestrogen agent to tamoxifen.

Claims 14-22 and 62 encompass determining clinical outcome in human subjects of any age, ethnic population, and gender based solely on the observed ratio of the mRNA expression levels any HoxB13 sequence and any IL17BR sequence, where any expression level ratio higher than the average ratio of HoxB13 and IL17BR RNA expression levels in ER(+) breast cancer cells is indicative of cancer recurrence. The methods of claims 14-22 are also not limited to

patients having ER(+) breast cancer and comprise treatment of the subjects with any antiestrogen agent. Claims 52 and 53 further limit the HoxB13 and IL17BR sequences to SEQ ID NO: 6 and SEQ ID NO: 1, respectively. Claim 68 further limits the antiestrogen agent to tamoxifen.

The methods of claims 23-31 and 63 encompass predicting the response of ER(+) breast cancer human subjects of any age, ethnic population, and gender to treatment with any antiestrogen agent based solely on the observed ratio of the mRNA expression levels any HoxB13 sequence and any IL17BR sequence, where any expression level ratio higher than the average ratio is indicative of a positive response to treatment. Claims 54 and 55 further limit the HoxB13 and IL17BR sequences to SEQ ID NO: 6 and SEQ ID NO: 1, respectively. Claim 69 further limits the antiestrogen agent to tamoxifen.

The methods of claims 32-34, 37, and 59 encompass determining the risk of cancer recurrence in human ER(+) breast cancer subjects of any age, ethnic population, and gender if treated with any antiestrogen agent based solely on any observed increase in the RNA or protein expression levels of any HoxB13 sequences (i.e. wild-type or mutant) or any observed decrease in the RNA or protein expression levels of any IL17BR sequences (i.e. wild-type or mutant). Claims 35, 36, 38, 42, and 60 further limit the method to mRNA expression levels, and claims 56 and 57 further limit the HoxB13 and IL17BR sequences to SEQ ID NO: 6 and SEQ ID NO: 1, respectively. Claim 70 further limits the antiestrogen agent to tamoxifen.

The specification teaches that the ratio of HoxB13 and IL17BR RNA expression can be used to determine a risk of cancer recurrence, predict clinical outcome, and predict the responsiveness of any human subject to treatment with an antiestrogen agent (see pages 9-12 and 55, for example). The specification also teaches that any change in the ratio compared to the

average ratio is sufficient for prediction and risk assessment (pages 17-18, for example). The specification further teaches that the methods can be used to predict the responsiveness of a subject to any antiestrogen agent (pages 15-16, for example). Finally, the specification provides a number of HOXBI3 and ILITBR sequences and teaches that "any sequence, or unique portion thereof, of the following ILI7BR sequence, identified by AF208111 or AF208111.1, may be used in the practice of the invention" and goes on to disclose the ILI7BR sequence of SEQ ID NO: 3 (see pages 34, lines 2-4 and SEQ ID NO:3 on page 34-35). Similarly, the specification teaches that "any sequence encoding all or part of the protein encoded by any ILI7BR sequence disclosed herein may be used (page 29, lines 4-10)."

In Example 1, the specification teaches that a 22,000-gene high-density oligonucleotide microarray was used to determine gene expression patterns from 60 ER+ breast cancer patients who were uniformly treated with tamoxifen (see page 60, line 20 - page 61, line 14). The ILI7BR and HOXB13 oligonucleotide sequences used in the microarray are undisclosed. In Example 2, the specification teaches that from the resulting data set, 5,475 genes were selected for further analysis and that using this reduced dataset, a t-test was performed on each gene comparing "the tamoxifen responders and non-responders, leading to identification of 19 differentially expressed genes at the P value cutoff of 0.001 (Table 2)", including HOXBI3 and ILI7RB (see page 65, lines 5-15). Then, to further refine the analysis, the specification teaches that the same cohort was reanalyzed following laser-capture microdissection of tumor cells within each tissue section and 9 differentially expressed gene sequences were identified with P0.001, again including HOXBI3 and ILI7BR (see page 66, lines 2-6 and Table 3). The specification teaches that HOXBI3, ILI7BR, and CACNAID expression levels were found to be significantly correlative in

both the LCM and whole tissue section samples (see, *e.g.*, page 67, lines 3-10). The specification further states that "...these three genes have potential utility for predicting clinical outcome of adjuvant tamoxifen therapy (page 68, lines 6-7)." Finally, the specification discloses that the HOXBI3 and ILI7BR expression ratio is a "strong independent predictor of treatment outcome in the setting of adjuvant tamoxifen therapy (see, *e.g.*, page 70, lines 5-7)."

However, the working examples do not teach the use of the HOXBI3 and ILI7BR expression ratio outside the setting of adjuvant tamoxifen therapy (*e.g.* to predict a risk of cancer recurrence or the responsiveness of a subject to any other antiestrogen agent). The specification also does not teach what levels of mRNA expression of HOXB13 and IL17BR sequences are required such that the ratio is indicative of responsiveness to a particular treatment, clinical outcome, or the risk of cancer recurrence. The working examples also do not analyze protein expression ratios of HoxB13 and IL17BR. The working examples also do not address the ability of the expression ratio to be used in different human populations (*e.g.* different ethnic populations, age groups, or male and female breast cancer patients) or whether the ratios of any different HoxB13 and IL17BR sequences can be used to predict the risk of cancer recurrence, clinical outcome, or responsiveness to antiestrogen treatment. Finally, the working examples do not describe correlating a lower than average HoxB13/IL17BR ratio with a lack of response to antiestrogen treatment as required by claim 23.

As a result, the specification does not adequately describe the claimed methods of determining the risk of cancer recurrence, clinical outcome, or responsiveness of any human subject to treatment with any antiestrogen agent based on the expression ratio of any HoxB13 and IL17BR sequences. As discussed above, the working examples are limited to a single

embodiment of the claimed methods conducted using a small sample size. The working examples do not extend the results to any other embodiments encompassed by the claims. In other words, the specification does not adequately describe a representative number of species within the very large genus encompassed by the claims. The specification also fails to teach the relevant identifying characteristics required to satisfy the written description requirement, since it contains no discussion of validation methods or strategies expected to be useful in determining which antiestrogen agents, human populations, etc are expected to be capable of functioning in the claimed methods. As discussed above, the claimed methods are associated with a high level of unpredictability, and as a result, the level of skill in the art required to practice the claimed methods is high. Also, as discussed above, the claimed methods were unknown in the prior art at the time of filing. Therefore, it must be concluded that Applicant was not in possession of the full scope of the claimed methods at the time of filing.

Double Patenting

9. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned

with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. Claims 6-22, 32-38, 42, 49, 50, 52, 53, 56-62, 67, 68, and 70 are rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 1, 2, 4-20, 29-39, and 41-43 of U.S. Patent No. 7,504,214 B2. Although the conflicting claims are not identical, they are not patentably distinct from each other, because the methods recited in claims 1, 2, 4-20, 29-39, and 41-43 of the '214 patent recite a species of the methods recited in the instant claims 6-22, 32-38, 42, 49, 50, 52, 53, 56-62, 67, 68, and 70. Accordingly, the methods recited in claims 1, 2, 4-20, 29-39, and 41-43 of the '214 patent anticipate the methods of the instant claims 6-22, 32-38, 42, 49, 50, 52, 53, 56-62, 67, 68, and 70.

11. Claims 6, 7, 9-15, 17-22, 32, 34-38, 42, and 58-62 are provisionally rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 1 and 9-27 of co-pending Application No. 11/089,097. Although the conflicting claims are not identical, they are not patentably distinct from one another, because the methods recited in claims 1 and 9-27 of the '097 application recite all of the limitations of the instant claims 6, 7, 9-12, 14, 15, 17-20, 32, 35, 36, 38, 42, and 59-62. Accordingly, the methods recited in claims 1 and 9-27 of the co-pending '097 application anticipate the methods recited in the instant claims 6, 7, 9-12, 14, 15, 17-20, 32, 35, 36, 38, 42, and 59-62.

The claims of the '097 application do not recite the limitations of the instant claims 13, 21, 22, 34, 37, and 58, which require analysis of particular samples. However, it would have

been *prima facie* obvious for an ordinary artisan practicing the methods recited in the claims of the '097 application to utilize any sample known to be useful for determining mRNA expression levels, such as the samples recited in the instant claims 13, 21, 22, 34, 37, and 58. An ordinary artisan practicing the method recited in the claims of the '097 application would have recognized that such samples were suitable for practicing the methods recited in the '097 application, and therefore, would have been motivated to analyze them with a reasonable expectation of success. As noted in MPEP 2144.07, it is *prima facie* obvious for one of ordinary skill in the art at the time of invention to select a known material based on its suitability for the intended purpose in the absence of unexpected results. In this case, no evidence has been presented to suggest that the use of the samples recited in the instant claims 13, 21, 22, 34, 37 and 58 is associated with unexpected results. Thus, claims 1 and 9-27 of the '097 application are not patentably distinct from the instant claims 6, 7, 9-15, 17-22, 32, 34-38, 42, and 58-62.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

12. Claims 6, 7, 9-15, 17-22, 32, 34-38, 42, and 58-62 are directed to an invention not patentably distinct from claims 1 and 9-27 of commonly assigned Application Serial No. 11/089,097. Specifically, as discussed above, the methods of the instant claims 6, 7, 9-15, 17-22, 32, 34-38, 42, and 58-62 are either anticipated by or an obvious variant of the methods recited in claims 1 and 9-27 of the '097 application.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300).

Commonly assigned Application No. 11/089,097, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

Response to Arguments

13. Applicant's arguments filed on September 20, 2007 regarding the rejection of claims 6-38, 42, and 52-66 under 35 U.S.C. 112, first paragraph (written description) have been considered, but they are moot in view of the new grounds of rejection presented above.

Applicant's arguments filed on September 20, 2007 remain pertinent to the new grounds of rejection above in which claims 6-38, 42, 49, 50, 52-63, and 67-70 are currently rejected for failing to comply with the enablement requirement of 35 U.S.C. 112, first paragraph. These arguments have been fully considered, but they were not persuasive.

Applicant first argues claims are presumed to be enabled unless there is an objective reason for doubt, and that the required objective reason for doubt has not been articulated (see

pages 15-16). This argument was not persuasive, because as discussed in greater detail above, the teachings cited in the art clearly establish an objective reason for questioning whether the claimed methods are enabled by the disclosure.

Applicant also argues that no more than routine experimentation is required to practice the claimed methods (page 17). This argument was not persuasive, because as discussed above, the cited references clearly establish that a very large quantity of highly unpredictable experimentation would be required to practice the full scope of the claimed methods. This requirement to perform a large amount of highly unpredictable experimentation with little guidance from the specification is by definition undue experimentation (see MPEP 2164).

Applicant also argues that teachings of the previously cited references do not establish a lack of enablement in the instant claims, because they do not pertain to the claimed HoxB13 and IL17BR expression levels (page 17). This argument was not persuasive, because the previously cited and newly cited references that do not discuss the claimed HoxB13 and IL17BR expression levels are relevant to the issue of enablement, because they establish and support the conclusions made in the rejection regarding the state of the art with respect to the use of RNA expression levels for cancer prognostics, the unpredictability in the art, the high level of skill in the art required to practice the claimed methods, and the quantity of experimentation necessary to practice the claimed methods.

Regarding the provisional rejection of claims 32-37, 42, 59, and 60 on the ground non-statutory obviousness-type double patenting citing co-pending Application Serial No. 11/089,097, Applicant requests that the rejection be held in abeyance until allowable subject matter is indicated in the instant application or the co-pending application (see page 18). This

rejection currently applies to claims 6, 7, 9-15, 17-22, 32, 34-38, 42, and 58-62. Since the provisional obviousness-type double patenting rejection is not the only issue remaining in either the instant application or the '097 application, the rejection has been maintained above in accordance with the guidance provided in MPEP 804.

Regarding the provisional rejection of claims 6-38, 42, and 52-66 on the ground non-statutory obviousness-type double patenting citing co-pending Application Serial No. 10/727,100, Applicant requests that the rejection be held in abeyance until allowable subject matter is indicated in the instant application or the co-pending application (see page 18). Since the '100 application has issued as US Patent No. 7,504,214 B2, the provisional rejection has been replaced with a formalized obviousness-type double patenting rejection in accordance with the guidance provided in MPEP 804.

Conclusion

14. No claims are currently allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANGELA BERTAGNA whose telephone number is (571)272-8291. The examiner can normally be reached on M-F, 9- 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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